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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/724,425	11/28/00	REED J	10412-026

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EXAMINER	
SCHMIDT, M	
ART UNIT	**PAPER NUMBER**
1635	6

DATE MAILED: 07/03/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev.11/00)

1- File Copy

Office Action Summary	Application No. 09/724,425	Applicant(s) REED, JOHN C.	
	Examiner Mary Schmidt	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-24 is/are pending in the application.

4a) Of the above claim(s) 1-7 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 8-24 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

KATRINA TURNER
PATENT ANALYST

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of Group II in Paper No. 5 is acknowledged. No ground(s) for traversal were provided. Therefore, the election is treated as non-traversed.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-7 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 5, filed 5-07-01.

Specification

2. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

In the instant case, the specification needs to be updated to include all parent cases and their current status.

3. The Brief Description of the Drawings on page 8 needs to include the sequence identifiers of the sequences in Figure 13.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 8-12, 15, 17 and 20-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8 and 10-13 are indefinite since claim 8 begins with "The method of treating a bcl-2 related disorder" instead of "A" method of treating. Since claim 8 does not depend on any other claims, it is not clear why the definite article "The" was used.

Claims 8, 9, 15 and 17 are incomplete since they lack a final step which relates back to the preamble.

Claim 10 lacks antecedent basis for "said one or more chemotherapeutic agents".

Claim 11 lacks antecedent basis for "said combination".

Claim 12 is indefinite for improper Markush language.

Claim 14 lacks antecedent basis since it is improperly dependent on non-elected claims 1-7.

Claims 20-22 are indefinite for the language "and derivatives thereof." As written the claimes read on an agent comprising all of the compounds. It appears the claim should read "or derivatives thereof."

6. Claims 8-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to methods of treating a bcl-2 related disorder via administering an effective amount of any anticode oligomer (herein referred to as antisense) wherein said antisense hybridizes to the nucleic acid sequence of SEQ ID NO:19 (a human bcl-2 gene); more specifically, methods of treating cancer such as from the group consisting of non-Hodgkin's lymphoma, prostate cancer, breast cancer, gastro-intestinal cancer or colon cancer; methods of increasing the sensitivity of tumor cells to chemotherapeutic agents; methods of killing tumor cells; and pharmaceutical compositions comprising said antisense which have implied therapeutic uses.

The specification as filed does not teach by way of example antisense administration to cells in whole organisms. However, the post-art (after 12/22/88) is replete with examples of bcl-2 antisense administration to cancer cells in cells in culture and in whole organisms such as murine.

Although it has been shown in the post-art that antisense to bcl-2 is effective at combating cancer in cancer cells in culture and in murines, the claims as written read broadly on use of any nucleotide which hybridizes to SEQ ID NO:19, of any unspecified length or oligonucleotide composition, and further wherein the claimed treatment is of any organism for any disorder related to bcl-2 expression. As such, the scope of the claimed invention in its breadth would lead

one of skill in the art to necessarily practice undue experimentation to make and use the claimed invention.

The state of the art with antisense continues to be highly unpredictable. In the instant case, although isolated examples are shown in the post-art, such examples do not provide a representative number of species for enablement of any oligonucleotide which could hybridize to SEQ ID NO:19 to be considered a suitable candidate as a therapeutic agent for any bcl-2 related disorder in any whole organism. The factors considered to be unpredictable are as follows: (1) The structure of the scope of possible antisense oligonucleotides which would hybridize to SEQ ID NO:19 is not known. Although several anti-bcl-2 oligonucleotides art taught in the post-art, they do not provide a representative number of species to function as antisense to any bcl-2 gene from any whole organism as broadly claimed.; (2) Although the post-art teaches particular anti-bcl-2 sequences which function in an antisense manner in cells in culture and in murine whole organisms, such examples do not provide a specific nexus or correlation for an expectation of success of these or other possible anti-bcl-2 compositions as therapeutic agents in cells in other whole organisms (such as human) for the scope of therapeutic functions claimed.

More specifically, there is a high level of unpredictability known in the antisense art for therapeutic, *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-

specific binding (see Branch). Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Flanagan teaches, "oligonucleotides (in vivo) are not distributed and internalized equally among organs and tissues.... Unfortunantly, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)."

Specifically, *in vitro* results with one antisense molecule are not predictive of *in vivo* (whole organism) success. *In vitro*, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." And in the instant case, the claims read broadly on administration of an antisense inhibitor in any cell, therefore the whole organism included. While the specification teaches cell culture inhibition, no evidence of successful *in vivo* (whole organism) antisense inhibition has been shown, nor do the culture examples correlate with whole organism delivery.

One of skill in the art would not accept on its face the successful delivery of the breadth of any possible anti-bcl-2 antisense molecules *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art. Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of antisense molecules in whole organisms. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo*, (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed.

Thus, although isolated examples are found in the post-art, they do not correlate to an expectation of those or other antisense oligonucleotides which would hybridize to SEQ ID NO:19 as therapeutic agents since each antisense oligonucleotide functions in a sequence specific manner, having a unique set of enablement issues when used as a therapeutic agent and differs further based on the particular whole organism, the nature of the disease, and routes of administration of the antisense oligonucleotide.

Therefore, it would require undue experimentation to practice the invention as claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Katrina Turner*, whose telephone number is (703) 305-3413.

M. M. Schmidt
June 27, 2001

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER